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(*Continued.*)

Prize Essay, for which the American Neurological Association Awarded $200.00 at its Annual Meeting, June 5, 6 and 7.

THE BIOLOGICAL AND MORPHOLOGICAL CONSTITUTION OF GANGLIONIC CELLS, AS INFLUENCED BY SECTION OF THE SPINAL NERVE ROOTS OR SPINAL NERVES. TO WHICH IS APPENDED SOME REMARKS ON LOCALIZATION.

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ALTHOUGH observations on ascending changes following lesion of peripheric nerves or of their roots are becoming more and more numerous, a perusal of the literature of this subject shows that a unanimity of opinion as to the extent and nature of these changes has not been reached. Indeed, one of the latest investigators, Vanlair, has attained results which seem to contradict all observations made heretofore. He states that unilateral section of a spinal nerve, whether a regeneration of the latter took place or not, is in no case followed by any alterations in the structure of the spinal cord. His conclusions are based upon the results of numerous neurotomies and amputations performed on full grown dogs which were killed from six months to two and a half years after the date of operation.

I mention these facts in order to demonstrate that the final word has not yet been spoken and that, therefore, I may be excused for taking the subject up again.

The older literature on this subject has been exhaustively treated by Homen, which allows me to make my review of it rather brief.

The anatomical material on which previous authors based their conclusions was obtained in various ways. The largest number of publications are descriptions of the alterations found in the spinal cord and nerve stumps of persons who had previously suffered the loss of a limb by amputation.

In one case (Edinger) the amputation had taken place before the birth of the patient, that is, the child was born without a forearm. In another case (Strümpell) compression of the cauda equina in a man furnished the pathological material. Other researches have been made by aid of the experimental method, comprising neurotomies, neurectomies, ligation of nerves, amputations, sections of nerve roots and similar operations.

As to the alterations following these various injuries, I shall first mention those found in the gray substance of the spinal cord, and in order to simplify the matter, I shall give some tables of the observations:

I. The gray substance was found entirely normal.

AUTHOR.	MODE OF OPERATION.	RESULT.
Buffalini et Rossi.	Section of spinal roots.	
Vanlair.	Amputations and neurotomies.	No alterations when the lesion was unilateral.

II. Both the anterior and posterior horn of the operated side showed a lessening of volume and change of shape.

AUTHOR.	MODE OF OPERATION OR PATHOLOGICAL CAUSE.	
Hayem.	Tearing off of sciatic nerve.	Chiefly anterior horn affected.
Hayem et Gilbert.	Amputation.	
Vulpian.	Amputations in man and neurotomies of sciatic nerve of rabbits.	
Reynolds.	Amputation	
Edinger.	Amputation in utero.	
Kahler and Pick.	Amputation	

Mayser.	Section and tearing off of sciatic nerve.	Chiefly posterior horn affected.
Marinesco.	Amputation.	Results different in different cases.
Dejerine et Mayor.	Amputation.	Posterior and anterior horn affected in equal proportion.

III. The alterations were limited to the anterior horn, while the posterior horn was found perfectly normal.

AUTHOR.	MODE OF OPERATION OR PATHOLOGICAL CAUSE.
Dreschfeld.	Amputation.
Dudley.	Amputation.
Genzmer.	Amputation.

IV. The changes were exclusively or nearly exclusively confined to the posterior horn and sensory tracts, and the anterior roots were normal or nearly so.

AUTHOR.	MODE OF OPERATION OR PATHOLOGICAL CONDITION.
Max Joseph.	Section of spinal nerves and of roots of spinal nerves.
Friedländer and Krause.	Amputations.
Bignamini and Guarnieri.	Amputation of thigh.
Kahler.	Section of spinal roots.
Strümpell.	Lesion of cauda equina.
Homen.	Experimental amputations.

The authors mentioned in the last table firmly maintain that section of motor fibres in the anterior roots or in the peripheric course of spinal nerves does not cause any ascending alterations of these fibres or of the nerve cells from which they take their origin.

Friedländer and Krause conclude that if the motor paths became atrophic in ascending direction, the atrophy should include the anterior roots, which, they state, was never the case in their observations. They, therefore, arrive at the conclusion that the ascending atrophy following the amputation of a limb is exclusively confined to the sensory tracts.

Max Joseph, Strümpell and Bignamini and Guarnieri confirm F.'s and K.'s opinion. Homen inclines very much to the same view, although he expresses himself somewhat less positively.

Hayem's conclusions are: "L' atrophie cicatrielle produite dans le faisceau postérieur de la moelle en dehors du cordon de Goll par l'arrachement d'un nerf détermine une atrophie très rapide des cellules nerveuses qui porte surtout sur le groupe du tractus intermedio-lateralis (postero-lateral group)."

This conclusion is rather peculiar since Hayem distinctly states that the anterior roots were also atrophic and that throughout the whole area of gray substance the nerve cells were atrophied. It would certainly seem more natural to connect etiologically the atrophy of the nerve cells in the anterior horn with that of the anterior roots instead of with that of the posterior roots. Homen, Friedländer and Krause, who examined the spinal cord of persons or dogs on whom amputation had been performed, also found atrophy or lessening of the number of cells in the postero-lateral group, but found only quite insignificant alterations (if any) in the cells of the other groups of the anterior horn. The atrophy of the postero lateral group had to be explained, of course, considering that the anterior roots were found normal. The explanation given by them is, that the cells of this group are most probably sensory, a view which finds some support in Lenhossek's observation. The latter's conclusions were based on observations made by the aid of Ramon y Cajal's method. He saw fibres originate from cells in the lateral part of the anterior horn and pass through the spinal cord, posterior root and spinal ganglion without becoming connected with cells of the latter.

Marinesco and Reynolds oppose the theory that the postero-lateral group has sensory functions.

That alterations of cells in the postero-lateral group have, indeed, been much more frequently and more constantly observed than changes of the cells of any other group, will be shown by the following table:

Atrophy or disappearance of nerve cells of the anterior horn was found by:

AUTHOR.	MODE OF OPERATION OR PATHOLOGICAL CAUSE.	CELL GROUPS AFFECTED.	
Dudley.	Amputation.	The antero-lateral and postero-lateral groups are those in which the difference is most evident.	Chiefly antero-lateral and postero lateral groups.

Friedländer & Krause.	Amputation.	The postero-lateral group is exclusively affected.	Exclusively or nearly exclusively postero-lateral groups.	Predominantly postero-lateral group.
Homen.	Amputation.	The postero-lateral group is nearly exclusively affected.		
Vulpian.	Amputation & section of sciatic nerve.	The postero-lateral group is predominantly affected.		
Hayem.	Tearing off of sciatic nerve.	Rapid atrophy of nerve cells, especially of the postero-lateral group.		
Mayser.	Section & tearing off of sciatic nerve.	The postero-lateral group is entirely absent.		
Marinesco.	Amputation of thigh or arm.	The postero-lateral group is principally affected.		
Hayem and Gilbert.	Amputation of thigh or arm.	The gray substance is nearly entirely deprived of nerve cells.		All groups.
Reynolds.	Amputation of thigh or arm.	All groups affected.		
Dejerine and Mayor.	Amputation of thigh or arm.	Only in one of four cases was there a lessening of the number of cells. It was stated in all three groups, but chiefly in the antero-internal one.	Chiefly antero-internal group.	
Kahler.	Amputation of thigh or arm.	Cell changes in all groups, but chiefly is the central one.	Chiefly central group.	
Vaulair,	Section of sciatic nerve.	Central group affected in one case.		
Erlitzky.	Amputation.	Lessening of the number of cells of the anterior horn.		
Genzmer.	Amputation.	The number of nerve cells of the anterior horn is lessened.		
Dickson.	Amputation.	The number of nerve cells of the anterior horn is lessened.		
Edinger.	Amputation during fœtal period.	Destruction of cells of the anterior horn.		

It is noteworthy that all cases in which the postero-lateral group was affected were taken from the spinal cord of persons or animals on whom amputations or section of peripheric nerves had been performed. In none of them had isolated section of the posterior or anterior roots been made. Singer and Muenzer and Rossolymo cut the posterior roots separately without injuring the anterior roots, but none of these authors mentions alterations of the cells of the postero-lateral group as a consequence of this operation. Rossolymo states that there was a decrease of the number of cells in the posterior horn of the operated side, but he says nothing about the postero-lateral group.

There is consequently sufficient reason to make it questionable whether the postero-lateral group has sensory functions. It must also be kept in mind, that in many cases of amputations or section of the sciatic nerve the principal alterations were found in the central (Vanlair) or antero-internal (Dejerine and Mayor), or antero-lateral group (Dudley, in whose case, however, the postero-lateral group was also much atrophied). Accepting Friedlander and Krause's theory, these groups must, therefore, have sensory functions, a conclusion which contradicts too seriously the findings in progressive muscular atrophy, poliomyelitis anterior, etc., to be accepted.

The condition of the affected nerve cells has been described as simple atrophy by many authors, as a degenerative atrophy by others. Besides the complete disappearance of cells which, of course, signifies the highest degree of atrophy or degeneration, decrease in size of the cells, shrinking or disappearance of the processes, alterations of the nucleus and abnormal staining have been observed. I have met with only three cases in the literature where hypertrophic or pseudohypertrophic conditions of presumably motor cells were mentioned to be the secondary effect of a lesion. Of these three cases only one can properly be used for comparison, as in the two others the lesion which called forth said condition was situated in the spinal cord itself. However, all three cases are interesting enough to be mentioned:

The first case is described by Mayser and relates to the spinal cord of a rabbit, in which immediately after birth a segment of the spinal cord in the dorsal region had been extirpated. Just how long after the operation the animal was allowed to live is not specified. The lumbar enlargement of the cord showed the following characteristics: "The gray substance has remained in an undeveloped state, the nerve cells are all larger than normal cells, less stained, pale, with soft, so to say, hydropsically swollen protoplasm and enormously swollen nuclei."

The second case, reported by Kahler and Pick, was a patient whose cervical spine had been fractured. The spinal cord was completely cut through at the height of the injury. The patient died twelve weeks after the accident.

In the lumbar enlargement the alteration of the white substance is confined to the changes caused by simple degeneration of the pyramidal tracts. Otherwise the white and also the gray substance appear normal with the exception, that some of the cells in the anterior horn have a pale, swollen appearance.

The third case is also reported by Kahler and Pick. The primary lesion was amputation of the left leg in the lower third of the thigh. Death was caused by cyanide of potash poisoning eighteen years after the date of injury. In the lumbar enlargement the following remarkable condition was present:

"There is a peculiar type of nerve cells in the anterior horn of the left side. These cells are decidedly enlarged by an increase of their contents. This is demonstrated by their round shape, and especially by the fact that the parts which are situated between the processes of the cells are not concave as in normal cells, but convex."

The cells mentioned appear paler and stained much more evenly by carmine than the normal cells of the other side. They have a homogeneous colloid appearance. The nuclei with very distinct nucleoli are located quite peripherically. They show off very distinctly, and in some sections appear like a projection attached to the cell. The mass of pigment is crowded towards the base of a process. The processes themselves show a normal appearance.

Nowhere are there signs of an inflammatory process to be seen.

The largest number of cells of the described type are found in the external (postero-lateral) group; they are less numerous in the medial (central) group, while there are none in the anterior group.

Aside from this hypertrophic or pseudohypertrophic condition one notes atrophy and disappearance of cells, that is, a lessening of the number of cells in all groups of the anterior horn. Atrophy and hypertrophy of cells alternate in such a manner, that evidently the same cause (amputation, section of the motor nerve fibres) produced hypertrophic (?) changes in part of the "motor" cells, atrophic in the others, unless the hypertrophy represents the primary stage of the changes which in other cells led to atrophy or complete disappearance.

The cases related heretofore—with the exception of the two cases of injury to the spinal cord—concern lesions of spinal nerves or of their roots. Lesions of cerebral motor nerves have been produced in different manners, viz., by section, excision, ligation, tearing off from the base of the brain, etc. (Gudden, Forel, Mayser, Ganser, Darkschewitsch and others). They always effected secondary alterations in the nerve cells from which the injured motor fibres took their origin. These alterations consisted in a shrinkage, which in the newborn led to a complete disappearance of the cells, while in the adult it was less pronounced; the intensity of the retrogressive process varying with the distance of the point of lesion from the motor centre in question, with the age of the animal and with the length of the interval between the injury and the death of the animal. Cell changes of a hypertrophic character in the centres of cerebral motor nerves have not been reported. Of the structural changes which can be discerned by the use of Nissl's method I shall speak later on.

So much for the observations on the structure of nerve cells as influenced by lesions of motor nerve fibres. It is not my intention to speak now of secondary degeneration occurring in the peripheric portion of severed motor fibres, but I wish to report the changes that have been noticed in the central (ascending) portion of the latter.

The following authors found the motor fibres of the stump, or at least the anterior roots corresponding to the injured nerve entirely normal:

AUTHOR.	MODE OF OPERATION OR PATHOLOGICAL CAUSE.
Vulpian.	Amputation and section of sciatic nerve.
Friedländer and Krause.	Amputation.
Kahler.	Section of both the anterior and posterior roots.
Dejerine and Mayor.	Amputation.
Max Joseph.	Section of nerves and of roots.
Bignamini and Guarnieri.	Amputation.
Strümpell.	Lesion of the cauda equina.

Dejerine and Mayor found changes in the central nerve stump of amputated persons, but stated that these changes did not reach up to the spinal cord, the roots being normal. Vanlair concludes that after an amputation or a neurotomy (whether regeneration takes place or not), an increase of the fine nerve fibres (fibres grêles) occurs which must not be ascribed to an atrophic or degenerative process, but to a proliferation of the pre-existing fibres. This process of proliferation was found to diminish in ascending direction and seemed to reach its upper limit at the point of emergency of the nerve from the spinal cord.

Other authors have found distinct atrophic or degenerative changes of the anterior roots of spinal nerves or of the intramedullary roots of cerebral nerves, as will be seen from the following table :

AUTHOR.	MODE OF OPERATION OR PATHOLOGICAL CAUSE.	CHARACTER OF CHANGES..	
Hayem.	Tearing off of sciatic nerve.	Atrophy.	Atrophic changes.
Bérard.	Amputation.	Attenuation of the roots. No microscopical examination made.	
Hayem et Gilbert.	Amputation.	Atrophy of extra medullary anterior and posterior roots.	
Dickinson.	Amputation.	Wasting of the nerve roots, especially of posterior.	
Dudley.	Amputation.	Fibres of anterior roots less numerous.	
Reynolds.	Amputation.	Anterior nerve roots smaller.	
Edinger.	Amputation in ultero.	Atrophy of sensory and motor roots.	
Genzmer.	Amputation.	Anterior roots thinner and containing less fibres	
Marinesco.	Amputation.	Distinct atrophy of the anterior roots in one case.	
Forel.	Lesions of cerebral motor nerves.	Marastic shrinkage of fibres of varying intensity, according to age of animals, etc.	Degenerative changes.
Marinesco.	Section of pneumogastric nerve in rabbits.	Decay of the medullary sheaths demonstrated with Marchi's method by the impregnation with numerous black granula.	
Darkschewitsch.	Lesions of spinal and cerebral motor nerves.		

In opposition to the view of Homen, Cossy and Dejerine and others, that if ascending changes took place as a consequence of injuries to motor nerve fibres they were of a purely atrophic nature, Forel had come to the following conclusions:

1. The motor nerve degenerates in the adult in both directions, the motor cells of its physiological centre being involved in the process of degeneration. This takes place when the nerve is severed at the base of the brain.
2. Section of the motor nerve in its peripheric course, provided that a regrowth of the nerve fibres into the peripheric stump is prevented, causes a slow marastic shrinkage of the nerve fibres in the central stump, and also of the nerve cells from which they take their origin.
3. There is no qualitative, but only a quantitative difference between secondary degeneration and the atrophy affected after Gudden's method. Both are actually processes of the same nature and consist in a necrosis of the injured element (neuron) in its whole extent.

Since Marchi's method became known Singer and Muenzer, Darkschewitsch, Marinesco and Moxaew (Mojieff) have applied it to verify, which view was correct; that is, whether the process occurring in the central stump of severed peripheric nerves should be called atrophy or secondary degeneration in the sense of Waller. As it is, the method used that decides Singer and Muenzer to oppose Forel's conclusions, I may be excused for giving a brief description of Marchi's method in its improved form.

The fresh specimen is cut into pieces not exceeding one cubic centimetre in size. These pieces are hardened in Müller's fluid for at least one week, but in no case longer than three months. Subsequently they are transferred to a mixture of one per cent. osmic acid (one part) and Müller's fluid (two parts) for from five to eight days, then washed out thoroughly in water during several hours and treated in the manner required for celloidin drenching.

By this treatment those nerve fibres which are in process of degeneration receive distinct differentiation. The degenerating nerve fibre is marked by the appearance of numerous black granula in its myelin sheath, which is evidently caused by a reaction of the osmic acid upon the decaying myelin. Normal fibres receive an evenly grayish or brownish appearance. Degenerating nerve bundles are consequently distinctly differentiated from their surroundings by the numerous black granula which they contain.

But only during the process of degeneration does this reaction take place. When degeneration has been fully established the products of degeneration being absorbed the reaction fails, and it becomes just as difficult to distinguish degenerated fibres from normal ones as with the carmine, nigrosine and similar methods, especially where normal and degenerated fibres are closely intermingled. The animals must, therefore, be sacrificed before degeneration has been fully established. Experience has shown that three to seven weeks after the date of the experiment is the proper time to kill them.

A thorough knowledge of the method is required, however, in order to avoid mistakes. The presence of black granula is not always indicative of degeneration. Singer and Muenzer have shown that when a normal nerve, after being removed from the body, is pinched or otherwise injured the same black granula will be found at the point of lesion. They also stated the presence of black granula in regions where degeneration could not take place and where the specimen had apparently not been damaged. Whether this may be explained by the disintegrating influence of the hardening process itself cannot be said at present, but it proves that one must not push the diagnostic value of the reaction which may properly be called "Marchi's and Algeri's reaction" too far. Singer and Muenzer are fully aware of this fact, but they also state that by repeating the experiments one can avoid errors. The degenerating fibres will always present a large number of the granula, and the latter will be found in the same region if the experiment is repeated, while where the appearance of the granula is accidental their localization will vary in every individual case. It is the constancy and intensity of the reaction that gives it diagnostic value.

Working with the above described method Singer and Muenzer reached the conclusion that wherever a nerve fibre is degenerating it must show Marchi and Algeri's reaction. If the latter is not observed at the time, when according to experience it should be present, there is no real degeneration. Judging from this point of view, they came to the conclusion that after the lesion of a peripheric nerve secondary degeneration occurs in the peripheric stump, but not in the central one. The alterations which take place in the latter they propose to call atrophy, when adults are concerned, or aplasia, when the newborn were operated upon.

Singer and Muenzer's statement is contradicted not only by Forel, but also by Darkschewitsch and Marinesco, although the latter authors applied the same method for their researches which S. and M. had used.

Darkschewitsch operated upon the facial, hypoglossal and sciatic nerves of full-grown guinea pigs. The nerves were cut or ligated or torn off of the medulla or spinal cord. The animals were killed six weeks after the date of the operation. The specimens were treated after Marchi's method. In spite of the variety of the experimental conditions the result was uniform: the roots of the cerebral motor nerves (VII., X., XII.), and both the anterior and sensory roots of the mixed nerve (sciatic) distinctly showed Marchi and Algeri's reaction in all cases operated upon.

To demonstrate the condition of the motor nerve cells as influenced by the injury D. repeated the experiments and hardened the specimens in Müller's fluid, staining the sections with carmine. He found a simple atrophy of the cells of the VII. and XII. centres. There was also a marked atrophy of the nerve cells in the anterior horn of the animals whose sciatic nerve had been operated upon, but it was less pronounced than in the other cases.

Marinesco cut the pneumogastric nerve of a half-grown rabbit (about two months old.) Three months after the operation Marchi and Algeri's reaction, viz., the appearance of numerous black granula, and chunks could be stated in the central stump of the nerve.

Mojieff (Moxaew) ligated the sciatic nerve of rabbits. The animals were killed three weeks after the experiment. M. then studied the changes both in the central and peripheric stumps, partly by treatment with osmic acid, partly by Marchi's method. He found distinct pathological changes in the ascending stump, but does not believe them to be identical with those found in the peripheric stump. While the fibres of the latter presented complete decay of the myelin sheaths, disappearance of the axis cylinders and proliferation of the nucle of Schwann's sheath, the anterior and posterior root fibres showed only the appearance of black granula their structure remaining normal otherwise. (No changes of the axis cylinders, no proliferation of the nuclei of Schwann's sheaths.) The appearance of the black granula, stated also in the roots of the healthy side, was pathological on the side of the operation by their larger quantity and larger size.

It can be seen from the above review of the literature that the opinions on the nature of the retrogressive process occurring in the central stump of a severed motor nerve are still divided. Thinking that further researches might clear the matter up, I resolved to add some casuistic material by aid of the experimental method.

I intended originally to study the condition of nerve fibres only, for which purpose I chose Marchi and Algeri's method, as the arguments put forth by these authors in defense of it seemed rather convincing to me. In the further course of my investigations I employed Nissl's method in order to study particularly the structure of the cells as influenced by the lesions created.

In selecting the physiologic anatomical material it first struck me that to my knowledge no author had used the dorsal nerves for the basis of his experiments, although many factors speak in favor of this choice. In the first place the area of the distribution of most dorsal nerves is well defined and anastomoses of one nerve with branches of another are exceptional; consequently the fibres of the central stump correspond to those of the peripheric one. In the sciatic and brachial plexus, however, anastomoses are so numerous that a proper comparison of the central with the peripheric stump cannot be made, the former containing quite other fibres than the latter. This is illustrated by the fact that according to Gowers the median and musculo spiral nerves derive their fibres from the same roots, viz., the fifth, sixth, seventh and eighth cervical. (To the formation of the musculo spiral nerve the fourth cervical root also contributes).

A similar proof is furnished by the interesting case which Müller reports. Here a lesion of the lowest two cervical roots caused a paralysis of all the motor and sensory nerves for the forearm and hand, while the functions of the nerves for the arm and shoulder remained perfectly normal. Or in other words: All branches of the cutan. brach. med., ulnar, median and musculo-spiral nerves which supply the forearm with

PLATE I.

FIG. 1. Dorsal portion (lower part) of a normal spinal cord of a young cat.

The illustration is a photograph showing the distribution of the ganglionic cells:—

Med = cells of the medial zone (Waldeyer's Mittelzellen).

Later. = group of the lateral horn.

Post. = group at the base of the posterior horn.

Magnifying power 47 lin. Vesuvine stain.

FIG. 2. Photograph. Normal anterior horn cells.

Magnifying power 260. Vesuvine stain.

PLATE I.

FIG. 1.

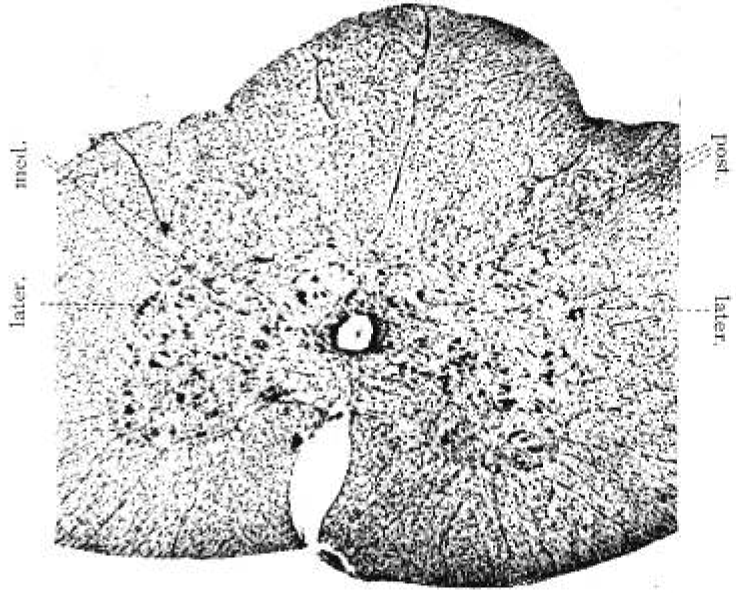


FIG. 2.

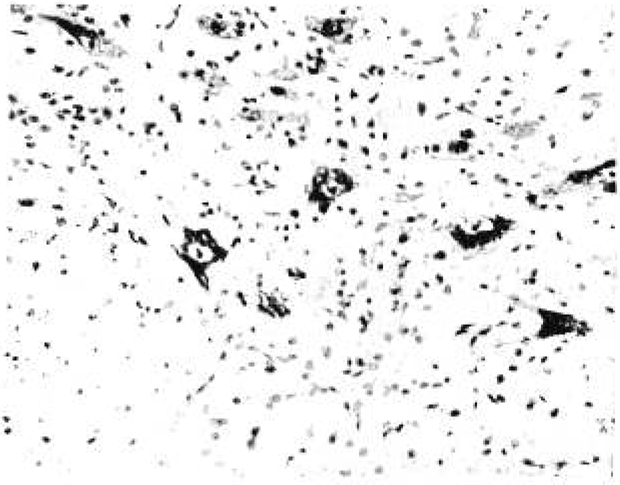


Fig. 1 reduced to $\frac{8}{11}$ of size of original plate, the magnifying power is therefore not 47 but 34 lin.

Fig. 2 reduced $\frac{8}{10}$, accordingly magnified 208 lin., not 260 as on original plate.

motor and sensory nerve fibres were paralyzed, while those branches of the same nerves which distribute their fibres in the arm remained perfectly normal.

The facts mentioned heretofore also bear reference to the distribution of the motor (and sensory) nuclei in the cord. It seems probable a priori that one dorsal segment functionally corresponds to the one dorsal nerve, while one segment of the cervical or lumbar enlargements corresponds to several peripheric nerves, these latter deriving only part of their fibres from this one segment.

What further complicates the conditions in the case of the sciatic or brachial plexus is that the lumbar and cervical enlargements having a more complex function, possess a larger number of association fibres and nerve elements which are in no direct connection with the nerves.

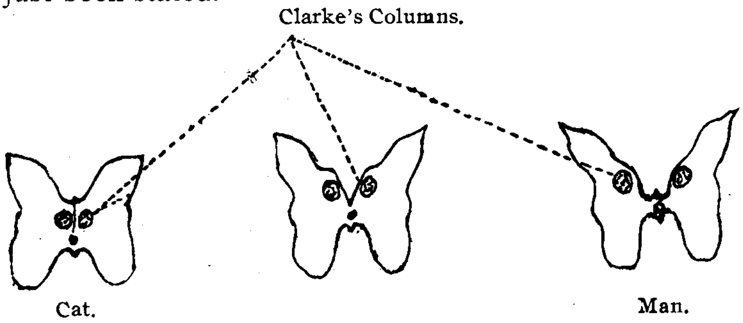
Having all these points in mind, I decided to select the dorsal nerves as a ground work for my experiments. The nerves operated upon were the eighth, ninth or tenth dorsal. In one case it was one of the lowest, but I did not mark exactly which. In all cases the experiments were performed on nerves of the left side. I chose cats for my experiments as the proverbial nine lives of those animals gave hope that most of them would survive the injury inflicted. A further advantage of experimenting upon cats is that the wounds heal rapidly, although not necessarily per primam intentionem. It is very important, of course, to proceed strictly aseptically, but although I observed the strictest asepsis during the operation I found it very difficult to keep up an aseptic condition of the wound later on. The bandages were usually sooner or later gnawed through or in some way torn off. So after several discouraging experiences with antiseptic bandages I finally decided to leave them off altogether. I sewed the wound up and removed the sutures twenty-four hours afterwards. If pus had formed in the meantime it would come out as soon as the sutures were removed. Under such circumstances I would sometimes reunite the wound by one or two sutures, but leave it sufficiently open to allow of a free discharge of the pus.

The age of the animals experimented upon varied between four and five weeks. As it was my intention to especially study the ascending changes of motor fibres, I began the series of experiments with isolated section of the anterior root of a dorsal nerve.

Before I enter upon the report of my observations, I wish to mention a few anatomical facts relating to the structure of the dorsal portion of the cord. In the first place it must be stated that the dorsal cord of the cat differs in several respects from that of the human cord, namely, in the shape of the gray commissure and in the location both of the central canal and of Clarke's columns. The gray commissure of the cat is comparatively much larger in a dorso-ventrad direction than that of man. In the human cord the central canal occupies the middle of the gray commissure, while in the cat it lies ventrad quite near its anterior (ventral) border, so that by far the largest part of the commissure is situated dorsad from the central canal. The median line of this enlarged dorsal portion of the commissure is marked by a sort of septum at both sides of which near the central canal Clarke's columns are located, while in man these cell groups are situated at the median border of the base of the posterior horn dorsad and somewhat laterally to the gray commissure.

This difference of structure is not as fundamental as would appear at the first sight, and if we imagine the dorsal part of the cat's gray commissure divided in the median line by a force which would crowd the severed portions laterally, the effect would be to equalize not only the width of the commissure, but also the location of the central canal and of Clarke's columns with those of man.

The following diagrams will best illustrate what has just been stated.



Another point of difference is given in the shape of the posterior columns, which in the cat appear larger in a dorso-ventrad direction, the posterior (dorsal) outline being more convex than it is in man. This might be explained by the increased width of the gray commissure which would naturally displace the posterior columns in a dorsad direction.

In other respects the dorsal portion of the cord of the cat is quite similar in structure to that of man ; but there are some points in which it differs from that of the lumbar and cervical portions of the cord.

I wish to call particular attention to the distribution of the ganglionic cells.

In the first place it needs mentioning that the division into groups is much less pronounced than in the lumbar and cervical portions of the cord. The best defined group is that of Clarke's columns, situated, as I have explained, dorsad from the central canal at both sides of the median line. Its cells are on the average smaller than the multipolar cells of the anterior horn, although varying quite considerably in size. They are frequently grouped in an oval or circle surrounding a stratum of nerve fibres. Occasionally one meets with a large solitary cell (mostly multipolar) situated exactly in the median line of the dorsal part of the gray commissure close by the central canal. The cell body of the cells of Clarke's columns usually presents itself in an oval or round shape with a large nucleus whose form varies with that of the cell. The number of processes is usually small.

Another rather well-defined group is that of the lateral horn. The latter is much less conspicuous than it is in the lumbar portion of the cord. It is marked only by a slight convexity of the lateral border of the gray matter. In many sections, however, triangular processes are seen projecting towards the lateral columns. The cells of said group are small, mostly of pyramidal or spindle, sometimes, as for instance, in Fig. 1, Plate I, of round shape. They are frequently crowded into nests arranged in a chain-like manner. The triangular processes mentioned are usually occupied by a crowded nest of cells. In location this group corresponds to the postero-lateral group of the lumbar enlargement, but its territory is much smaller. In the lumbar enlargement it is predominantly composed of large multipolar cells, while in the lateral horn of the dorsal cord large cells are rarely met with. It must further be stated that the group of the lateral horn of the dorsal cord shows off indistinctly against the surrounding parts, its cells becoming intermixed with those of the adjoining portions of the gray matter.

The antero-lateral, antero-internal and central groups are also represented in the dorsal portion of the cord, that is, we find large multipolar cells in the corresponding regions, but the arrangement varies so much that anatomical distinction of definite groups is hardly possible.

In that zone, which is situated between the base of the anterior and that of the posterior horn, and which might properly be called the medial zone, we find also numerous cells. Most of them are small or of medium size, of oval, spindle or pyramid shape; occasionally large multipolar cells are also seen. Quite frequently the smaller cells group in nests at the side of the central canal.

It but remains to mention one group of cells which I found to be quite constant. These cells are located between the bundles of nerve fibres, which, originating from the antero-lateral part of the posterior columns (mostly as a continuation of the median bundles of the posterior roots), pass in a curve through the base of the posterior horn towards the lateral columns.

The cells mentioned are usually very small, long-stretched, and their longitudinal axis coincides with the direction of said nerve bundles, between which they are arranged in chain-like tracts. Laterally these cells join the group situated at the lateral border of the gray substance between the lateral and posterior horns, which Bechterew calls the lateral group of the posterior horn. The cells of this latter group are, as a rule, much larger than those mentioned before, and mostly polygonal.

Having mentioned already that my first experiment consisted in isolated section of the anterior root of a dorsal nerve, I shall now give a description of the case:

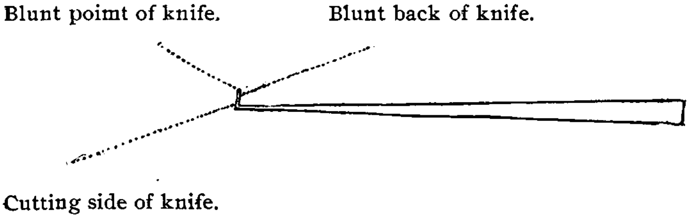
I.—Cat, 33 days old. Section of the anterior root of one of the lowest dorsal nerves of the left side (which nerve it was, cannot be exactly stated).

Experiment performed under ether narcosis.

Longitudinal incision over process. spinos. of vertebræ about one and one-half inch in length. Severing of insertion of muscles from the spinal column.

Resection of a piece of the covering of the vertebral canal by making two longitudinal sections with the saw about two mm. laterally from the process. spinos. and each measuring about one inch in length. Removal of the loosened piece with the bone forceps. I preferred this manner of proceedure to using the bone forceps exclusively, as in the latter case the bleeding is much more profuse.

The vertebral canal now being opened, I waited until the bleeding had entirely ceased, then removed the blood coagula partly by irrigation with sterilized water and partly by gently withdrawing them with the forceps. The roots were then exposed by removing the fat tissue that covers them. Some slight bleeding occurred again which ceased very soon. I then removed the blood coagula in the manner mentioned and proceeded to the section of the root. This was done with a small slender knife devised especially for that purpose. The following drawing will better explain this instrument than a lengthy description.



The knife was introduced between the two roots, after which the anterior root was pressed ventrad against the bone and cut through. The wound was then irrigated and sutured.

The animal was quite lively after the effects of the narcosis had passed over. At no time did it show any symptoms of shock or injury to the spinal cord. The gait was perfectly normal. The wound healed by secondary reunion. Four weeks after the date of the experiment the cat was killed by desanguination.

Examination revealed a cartilage-like covering of the vertebral canal at the locus of operation. After removal of this, covering tracts of a tissue similar to "jelly" in appearance and consistency were observed which formed adhesions between the dura mater of the cord and the vertebræ. These adhesions were easily removed without damage to the membranes which appeared normal.

The spinal ganglion that corresponded to the operated root was found embedded in a jelly-like mass of tissue, from which it was not possible to separate it. The posterior root seemed macroscopically normal. The anterior root which passed directly into the jelly-like mass just mentioned, was found transformed into a thick bundle of a soft, jelly-like tissue.

A piece of the spinal cord measuring about one and one-half inches in length and containing the segment which corresponded to the severed root was put in Müller's fluid for the purpose of preparing it for handling by Marchi and Algeri's method. I did not find it necessary to cut it into smaller pieces, as the thickness of the cat's spinal cord is only about one-half centimetre in this region. The peripheric nerve was also put into Müller's fluid. Both spinal cord and peripheric nerve were afterwards treated according to the directions of Marchi and Algeri, whose method I have described in some detail on page 606.

MICROSCOPICAL EXAMINATION.

1. Of the nerve:

It shows typical degeneration, the medullary sheaths of its fibres being impregnated with a large number of black granula and chunks. For comparison the corresponding nerve of the other side and other dorsal nerves were used.

2. Of the spinal cord:

A continuous series of about 450 transversal sections was made, each section varying in thickness from one-fortieth to one-eightieth mm. I shall now first describe the appearance of normal specimens which were treated after Marchi's method.

The white substance has microscopically a dark gray or brownish, the gray substance a light yellow or gray tinge. Microscopically the transverse sections of nerve fibres show a rather distinct differentiation of axis cylinder and medullary sheath, the former being of a dark greenish or black, the latter of a light gray color. On longitudinal sections of fibre bundles the axis cylinders appear as dark lines which show off rather distinctly against the lighter colored medullary sheaths. In the gray substance this differentiation is much less pronounced. (The appearance presented by the ganglionic cells I shall have occasion to describe later on). Here and there black granula or masses are seen scattered between the nerve fibres; their arrangement is quite irregular; occasionally, however, one will be found to correspond to the transversal section of a nerve fibre. They are chiefly located in the white substance; in the gray matter they are rarely met with. The localities in which these masses and granula are most frequently observed are the direct horizontal bundles of the posterior and anterior roots.

Let us now take the transverse sections of the level which corresponds to the severed anterior root.

I. WHITE SUBSTANCE.

The posterior column of the left side is much narrower than that of the right side. This lessening is due to a lessening of the entering posterior rootlets and of their continuation into the zone of vertical fibres situated laterally from the median border of the left posterior horn (medial fasicle of the posterior roots. Bechterew). The medullary sheaths have disappeared to a great extent, and the axis cylinders are crowded together so that they can hardly be distinguished from each other. Aside from this a large number of black granula are seen in said zone, viz., along the median border of the left posterior horn, while on the right side only a few are observed in this area. The presence of the few granula on the right side must be considered as accidental, while on the left side their large quantity and constancy is indicative of degeneration. This degeneration of the left posterior root was, of course, uncalled for, probably it was caused by the proliferation of interstitial tissue in which the posterior root and spinal ganglion were found imbedded.

The anterior roots of the left side present a considerable number of black granula and masses, but these are just as numerous in the anterior roots on the right side. Indeed, in spite of a careful examination of a large number of sections I could not notice any difference between the anterior roots of the right and those of the left side. If there was any degeneration I could not prove it by Marchi's reaction.

The antero-lateral columns of the left side are exactly like those of the right side. No signs of degeneration can be discovered.

II. GRAY SUBSTANCE.

As I have explained, the purpose of Marchi and Algeri's method is to produce a reaction which enables us to recognize the process of degeneration in nerve

PLATE II.

Illustrates the retrogressive cell changes observed four weeks after the section of the anterior root of a dorsal nerve of a young cat. Treatment of the specimen after Marchi's method.

FIG. 1. Water color.

Magnifying power 47 lin.

FIG. 2. Water color.

Magnifying power 320 lin. Showing various stages of the retrogressive changes.

PLATE II.

FIG. 1.

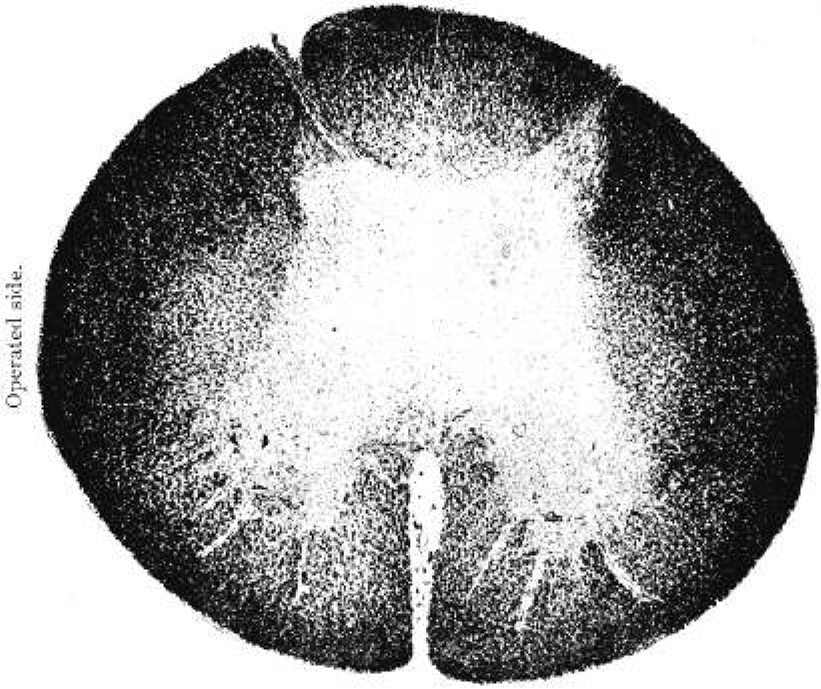


FIG. 2.

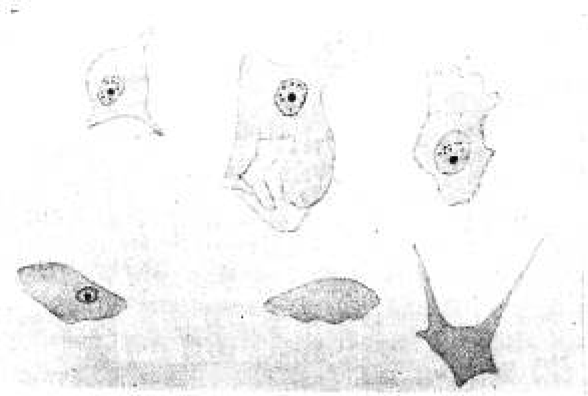


Fig. 1 reduced to $\frac{10}{17}$ of size of original illustration, the magnifying power is accordingly not 47 but 28 lin.

In Fig. 2 the reduction is very slight.

fibres: it has not been used to my knowledge for the recognition of cell changes. Indeed, Darkschewitsch, who, besides studying the degeneration of nerve fibres with Marchi's method, who wanted to get information on the condition of nerve cells as influenced by injuries of peripheric nerves, repeated his experiments, and after hardening the specimens in the usual way with Müller's fluid, stained the sections with carmine. That the method was not meant for defining the condition of cells is also clear from the fact that no author even mentions what appearance the ganglionic cells of "Marchi-specimens" show.

My observations, however, induce me to pay special attention to this point.

In sections of normal specimens that were treated after Marchi's method the cell, have a shrunken appearance, they are so badly differentiated from the surrounding tissue that with weak magnifying power (50 lin.) at first no cells whatever are distinguished. By looking more closely one will observe spots of irregular shape which are somewhat darker than the surroundings. With a stronger magnifying power (300) these spots can be identified as cells, which, however, show quite a rudimentary shrunken chunk-like appearance. Seldom can a differentiation of nucleus and nucleolus be made; the processes are sometimes present, but are also shrunken and rudimentary, more frequently, however, they cannot be recognized altogether, the cell being represented as a structureless mass. After having been examined with a strong magnifying power the cells are also recognized with a weak power, or, better said, they can be guessed at.

It is evident, therefore, that normal ganglionic cells receive a very poor differentiation by Marchi's method.

Let us see how the ganglionic cells which correspond to the injured anterior root present themselves in our specimen:

In examining the left anterior horn at the level of the injured root we see a considerable number of large cells with well-defined outline, distinctly differentiated nucleus and nucleolus and more or less developed processes. In comparing them with normal cells stained after Nissl's method, we find them considerably enlarged. This increase in size is due to a swelling which manifests itself by their rounded shape, the outlines of the cell body between the processes being convex instead of concave as in the normal cells. The swelling also involves the nucleus and the processes which latter mostly have a thick clumsy appearance. In many cells the processes look as if broken or fallen off, representing short thick stumps.

As I have mentioned, the outline is well defined in most of the cells, but one finds others in which it is blurred, so that the cell body can be properly compared to a half dissolved piece of celloidin or gelatin.

Some cells of the latter type will still present a well differentiated nucleus, in others the nucleus seems to have dissipated itself in the cell body altogether, although the nucleolus, which evidently preserves itself longest, may still be distinguished.

On the other side, but less frequently than the type just described, are seen cells with a sharp outline and rather well-developed processes, but without nucleus and nucleolus.

Occasionally we find a cell in which part of the cell-protoplasm has another appearance than the rest of the cell body; it looks as if a foreign body was located in the cell.

These various cell types represent various stages of the same pathological process, namely, of a homogeneous degeneration. This degeneration begins in the cell body (as I shall demonstrate later on) and then gradually involves the other parts of the cell, usually first the processes, then the nucleus, and finally the nucleolus, sometimes, however, first the nucleus and then the processes.

The earlier stages of the degeneration are marked by swelling and by distinct differentiation of the degenerating parts with Marchi's method. In later stages a sort of liquefaction evidently occurs by which the differentiation becomes lost in such a manner that single parts of the nerve element may still retain distinct differentiation and seemingly normal structure when the others are destroyed already.

In location and shape the described degenerated cells correspond to the large multipolar cells of the anterior horn, which are considered to have motor functions. The degenerated cells are most numerous in the left anterior horn, but also met with in the right one, the proportion being more or less three (side of operation) to one (other side). They are distributed over all groups of the anterior horns.

We find then, that the section of the anterior root of a dorsal nerve in a young cat produced within four weeks a degeneration of the large multipolar cells of the anterior horns, cells to which we ascribe motor functions. This degeneration must be called a homogeneous degeneration from reasons which I shall explain later. The beginning stages of said degeneration are characterized by a swelling of all parts of the cell and by their distinct differentiation with Marchi's method in contrast with normal cells which receive a very poor differentiation and shrunken appearance with said method.

The observations published above seemed to me so suggestive that I resolved to endeavor to elucidate the matter by further investigations. It had occurred to me that the condition of "motor" ganglionic cells as influenced by injuries of motor fibres had never been studied, yet at early periods after the experiment, but always at a time when the retrogressive process had presumably reached its final stage. It then occurred to me that possibly the described "pseudohypertrophic" condition of the anterior horn cells represented an early stage of degeneration which finally would lead to atrophy or complete disappearance of the cells. To determine whether my conjecture was justified, I decided to start a new series of experiments, to kill the animals at different periods after the experiment and to study the condition of the ganglionic cells with a method by which presumably the finest details of the cell structure could be discerned. Nissl's stain seemed to be the most fit and reliable for that purpose. Nissl's publications on the cell alterations of the VII. nucleus following the injuries of the VII. nerve were not known to me at that time; indeed, while collecting the literature on the subject in question I sought for his first publication regarding the facial nerve, which I found cited by various authors, but did not discover it until lately. I can say, therefore, that the following investigations were made quite independently, without knowledge of Nissl's observations. I am indebted to Dr. Spitzka for having called my attention to Nissl's second publication concerning the facial nerve, which indirectly led me to the discovery of his first publication. Having made my investigations without knowledge of Nissl's researches, it was so much more gratifying to me, that his results concerning the facial nerve coincide in the essential points with those which I obtained by operating upon the dorsal and intercostal nerves.

I am sorry not to have used Nissl's improved method for my researches as its publication had also escaped my attention. I employed his old method as described in the second edition of Obersteiner's "Anleitung zum Studium der nervoesen Central-Organe," but with certain modifications which will be seen from the following description:

Hardening of the fresh specimen in ninety-five per cent. alcohol from about one to two weeks, then in absolute alcohol for a further week, subsequently drenching with xylol for one day, then with solutions of paraffine in xylol of increasing concentration (until saturated) for about three or four days; finally drenching in melted paraffine at a temperature not exceeding the melting point, that is, at about 110° F. for two hours.

The sections were stained upon the slides in the following manner:

Fastening of the sections upon the slides by means of a mixture of rapidly filtered egg albumen and glycerine at equal parts (after P. Mayer). Smoothening of the sections with a moistened camel's hair-brush until they are quite even and adhere so firmly to the glass that pressure with the brush cannot displace them any more. The superfluous fixing fluid thus pressed out is wiped off from the slide. This done, a few drops of xylol poured over the section quickly dissolve the paraffine; this process is repeated, after the xylol first put on has been wiped off, until every trace of paraffine is out of the section. In the same manner the xylol is washed out of the section with absolute alcohol. Presently the slide is first transferred into water or directly into the staining fluid, a concentrated aqueous solution of vesuvine, wherein it is kept for about one hour (I made this modification, because by heating the sections shrivel). The superfluous staining fluid is subsequently washed out by putting the slide into water for a few seconds, keeping it longer in water does no harm. The water having been wiped off from the slide a few drops of alcohol are poured over the sections. The alcohol must be kept on long enough to abstract all water out of the sections which it does in a few seconds; keeping much longer will spoil the stain. The next step is to wipe off the alcohol and pour oil of cloves on the sections. The effect of the differentiation in the oil of cloves can now be watched directly under the microscope, which is a great advantage in my modification. (The mounting of the sections is best done by Nissl's benzine-colophonium method, as later experiences have shown me.)

Comparison of my "paraffine" sections with sections of a specimen which did not undergo the paraffine drenching, but was cut right after the hardening in alcohol, convinced me that the process of paraffine drenching did not damage the structure of the cells. I also compared the cell stain of my "paraffine" sections with the drawings of nerve cells with Alzheimer, who employed Nissl's improved methyl blue method gives in his monograph mentioned at the end of this article. This comparison proved that the cell structure as presented in these drawings does not differ from that which I found in my "paraffine" sections. I feel justified, therefore, in concluding that my modifications did not impair the results of the stain.

It would lead too far to give a detailed description of the structure of the various types of ganglionic cells as differentiated by Nissl's stain. Nissl himself has described them so accurately that I need only call attention to his numerous publications on that subject (Vide literary register at the end of this article), I shall but mention the essential points:

Nissl's stain reveals the existence of two parts in the substance of the cell body, one of which accepts the stain "chromatophile part of the substance," while the other remains unstained. Of the chromatophile part of the substance one portion becomes intensely stained, the other but slightly.

The intensely stained part is represented by the "corpuscles" of various shapes. In longitudinal cells spindle-shaped and stripe-like corpuscles prevail, in others, round, oval, angular and irregular forms are chiefly found. In many cells—and especially is this the case in the large multipolar cells of the anterior horns—these corpuscles are arranged in rows which in the vicinity of the nucleus have a tendency to run parallel with the outline of the latter, while in the peripheric part of the cell they mostly run parallel with the outline of the latter. In longitudinal cells they are usually more or less parallel with the longitudinal axis of the cell. In the processes the corpuscles appear in the shape of spindles, long-stretched pyramids or stripes, the longitudinal axis of which is directed parallel with that of the outline of the process.

To many cells, for instance to the large multipolar cells of the anterior horns, this arrangement gives an appearance similar to that of the tiger hide (Nissl. [See Plate I., Fig. 2].

The slightly stained part of the substance is more delicately organized and shows itself in the form of minute grains, finest threads, chains of minute grains, net works of finest threads, etc.

I shall now return to the subject in question and enumerate the experiments performed.

As mentioned before, the age of the cats upon which I experimented varied between four and five weeks:

Experiment 1.—Section of the anterior root of the left ninth dorsal nerve. Animal killed three days after operation.

Experiment 2.—Section of the anterior and posterior roots of the left eighth dorsal nerve. Animal killed six days after operation.

Experiment 3.—Section of the anterior root of the left eighth dorsal nerve. Animal killed fourteen days after operation.

Experiment 4.—Section of the left tenth intercostal nerve. Animal killed three days after operation.

Experiment 5.—Section of the left ninth intercostal nerve. Animal killed six days after operation.

Experiment 6.—Section of the left tenth intercostal nerve. Animal killed fourteen days after operation.

The intercostal nerves were severed peripherically from the dorsal branch which supplies the muscles of the back. Experiments 2 and 6 were performed upon the same animal. Experiments 3 and 4 were also performed upon one animal. For experiments 1 and 5 two separate animals were used.

In cases 1, 3 and 6 changes were found which could hardly be the result simply of the lesion intended, but were evidently partly caused by an abnormal inflammatory proliferation of the neuroglia elements. In one case (VI.) a kind of area of softening formed. In case IV. the series of sections was not complete and the stain deficient.

The clearest and most distinct results were those of Experiment II and V. I shall, therefore, first report these, and then mention as much of the others as may serve to corroborate the observations made in cases II and V.

EXPERIMENT II.—Section of the anterior and posterior roots of the left eighth dorsal nerve. Animal killed six days after the operation.

After the operation the animal showed some ataxy in the movements of the hind legs and a tendency to fall over when making a sharp turn. The symptoms disappeared within a few hours; afterwards the animal was very lively, played with the other cats, ran and jumped with much grace and skill, etc. The wound healed partly by primary and partly by secondary reunion. The cat was killed with chloroform six days after the date of the experiment.

Examination of the region of operation revealed that both roots had been entirely severed, and that the ends of the peripheric stump were so far removed from those of the central one as to surely exclude the possibility of a reunion.

MICROSCOPICAL EXAMINATION.

As with Nissl's stain the outlines of the gray substance became very indistinctly marked, some of the sections were stained with carmine. These sections show that the left posterior column is larger than the right one, both in dorso-ventrad and frontal direction. The region which corresponds to the tract of Lissauer seems also enlarged (although on account of the alcohol hardening which renders the structure of the nerve fibres very poorly, its recognition from the adjoining zones becomes very difficult).

This increase of volume of the left posterior column is evidently due to beginning degeneration of the posterior root zones. It seems natural to assume that in the beginning of the degeneration a swelling of the medullary sheaths occurs which would satisfactorily explain the increased volume of the left posterior column.

The antero-lateral columns are equal on both sides.

There is an asymmetry of the gray matter. The left posterior horn looks as if compressed in a radial (from apex towards central canal) direction, having a hemispherical shape. Its apex is much further removed from the dorsal periphery of the cord than that of the right one. Whether a difference in volume exists between the posterior horns, it is hard to decide on account of the asymmetry mentioned.

The left anterior horn is longer (ventro dorsal), but

PLATE III.

(Exp. No. II.) Illustrating the alterations which follow the section of the anterior (and posterior) roots of a dorsal nerve within six days.

FIG. 1. Photograph showing the dimensions of the gray and white matter.

Magnifying power 13 lin. Carmine stain.

FIG. 2. Photograph of a normal anterior horn.

Magnifiying power 111 lin. Vesuvine stain.

FIG. 3. Photograph of the anterior horn, the cells of which show homogeneous degeneration.

Magnifying power 111 lin. Vesuvine stain.

n is a normal cell, the others are degenerated.

FIG. 4. Water color, showing various stages of the homogeneous degeneration.

Magnifying power 320 lin. Vesuvine stain.

a. Cells presenting a circumscribed area of homogeneous degeneration of the cell body, the periphery of which has still a distinctly granular structure. Nucleus apparently normal in one cell, in the other only the nucleolus is still preserved.

b. Cells in which the nucleus has partly left the cell body.

c. Swollen cells, in two of which the nucleus is becoming dissolved in the cell body.

d. Late stages of the homogeneous degeneration, two cells represented only by structureless chunks.

PLATE III.

FIG. 1.

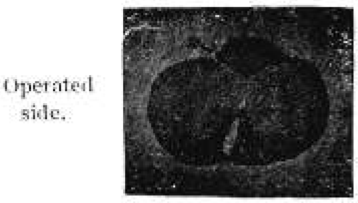


FIG. 2.

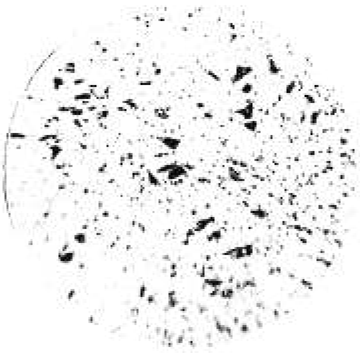


FIG. 3.

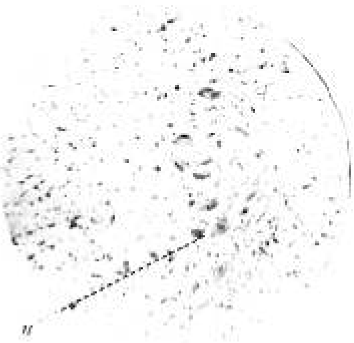


FIG. 4.

Fig. 1 reduced to $\frac{2}{3}$ of size of original illustration.
Figs. 2 and 3 reduced to $\frac{7}{11}$ of size of original illustration.
Fig. 4 reduced to $\frac{4}{5}$ of size of original illustration.

The magnifying power is accordingly—

For Fig. 1=9 lin. (not 13).
For Figs. 2 and 3=77 lin. (not 111).
For Fig. 4=256 lin. (not 320).

narrower (frontal) than the right one. This asymmetry seems to be caused by distortion; there does not seem to exist a difference in volume between the two anterior horns, although also here it is rather difficult to make a decision on that point.

No signs of inflammation are noticed anywhere. There is an increase of neuroglia elements in the left lateral horn, part of the cells of which are nearly buried under granular cells. Aside from this a proliferation of neuroglia elements is not noticed, especially not in the anterior horns.

There is a considerable lessening of the number of cells of the left column of Clarke and of the small cells of the left lateral horn. A large part of the remaining cells of these groups are shrunken, intensely stained and otherwise altered. Changes of the same nature are seen in cells of the zone situated between the basis of the left anterior and posterior horns (medial zone) and in many of the cells located at the base of the left posterior horn, a description of which group I gave in a previous section.

On the right side changes of the nature just mentioned are also observed in cells of Clarke's column, of the middle zone (between bases of anterior and posterior horns) and of the group at the base of the posterior horn.

The most conspicuous alterations of structure were found in the

LARGE MULTIPOLAR CELLS OF THE LEFT ANTERIOR HORN.

The most important features of the changes are succinctly stated in the following summary:

1. The differentiation of the chromatophile and chromotophobe parts of the substance of the cell-body is lost. The cell-body has a homogeneous appearance.
2. The homogeneous cells have a pale color.
3. The homogeneous transformation is usually, although not necessarily accompanied by a swelling cf the affected parts.
4. The processes undergo the same transformation as the cell-body.
5. The nucleus and nucleolus also undergo retrogressive changes; they finally become absorbed in the cell-body or the nucleus leaves the cell-body and probably becomes absorbed outside of the latter.

6. The degeneration evidently begins in a circumscribed part of the substance of the cell-body; the degenerated area then increases involving gradually the other parts of the cell.

7. The final result of the homogeneous degeneration is probably a liquefaction and absorption by endosmosis or by means of granular cells, although the degeneration may be arrested before this final stage is reached.

8. The cells thus affected are the large multipolar cells of the left anterior horn. A small number of degenerated cells is also found in the right anterior horn.

9. The said degeneration is caused by the section of the anterior root of a dorsal nerve.

In many of the diseased cells the whole cell-body including the processes, has a perfectly homogeneous appearance, in others the centre is homogeneous while the peripheric part shows still one or several distinct rows of intensely stained "corpuscles" (a name which Nissl proposes instead of granula).

Friedmann first promulgated the view that the homogeneous degeneration which he calls "homogeneous swelling" begins in a circumscribed part of the cell-body and progresses centrifugally. I can only affirm the correctness of this view by my observations. In many of the affected cells indeed only a small circumscribed area of the cell-body is homogeneous, the remaining part of the cell including the processes and nucleus having the characteristic granulated or striped appearance which Nissl's stain gives them.

In a large number of the affected cells the nucleus shows apparently normal stucture, in others it has a peculiarly light and shining appearance, the minute granula which it normally contains being scarce and the outlines being sharply defined, better than in normal cells where they are frequently hidden from view by the intensely stained "corpuscles" of the cell protoplasm covering them. Most frequently the nucleus is dislocated towards the periphery, bulging the outline of the cell-body out so as to look like a projection attached to the cell. In several cells I could state an actual "luxation" of the nucleus, the greater part of it lying outside of the cell-body. Probabaly the nucleus becomes entirely eliminated from the cell-body in this manner and is absorbed outside of it. In many cells, however, only a nucleolus is seen or the outlines of the nucleus are so indistinct, blurred that they can hardly be recognized. In these cases the nucleus is probably absorbed by the cell-body itself. The nucleolus preserves itself longest.

I have mentioned that in many of the degenerating cells the processes show still a normal structure when the cellbody or part of it is adlreay homogeneous; in others they are swollen and look homogeneous, or they have fallen off, only short stumps being left, or they have disappeared altogether.

Cells without processes but with apparently normal nucleus are seen. On the other side cells with apparently normal processes but without nucleus or without nucleus + nucleolus are met with.

Finally one finds homogeneous chunks in which every trace of the nucleus, nucleolus and processes has disappeared. These latter formations, of course, represent advanced stages of the process of degeneration.

To sum up, a large number of the large multipolar cells of the left anterior horn and some of the right anterior horn have undergone retrogressive changes which are analogous to what Friedmann calls homogeneous swelling or homogeneous degeneration (homogene Schwellung, glasige homogene Entartung). The degeneration begins in a circumscribed part of the substance of the cell-body and progresses centrifugally; the processes usually are next involved, earlier than the nucleus and nucleolus, but there is no doubt that quite frequently the nucleus degenerates earlier than the processes. As in many cells the outlines of the cell-body are quite blurred, it seems very probable that in the later stages a liquefaction takes place which finally leads to absorption of the cell. One manner of absorption is certainly the being eaten up by granular cells. I could see this in the case of the cat on which section of the anterior root of a dorsal nerve had been performed, and which was killed three days after the experiment. Here I also observed homogeneous degeneration of multipolar cells of the anterior horn and could make out that many of the degenerated cells had quite blurred outlines and were quite "buried" beneath granular cells.

If we compare the cell changes mentioned with those which were found in the spinal cord treated after Marchi's method (section of anterior root of a dorsal nerve, vide page 620) we find that there is a considerable analogy. The swelling of the cells was less marked in the Nissl specimen, but this may be explained by the direct and therefore stronger action of the alcohol, while in the Marchi specimen hardening with Müller's fluid and osmic acid preceded the alcohol treatment. Otherwise the alterations were so similar that in my opinion the process must have been the same in both cases.

Nissl has studied the retrogressive changes which tearing off of the VII nerve from the base of the brain caused to take place in the cells of the VII nucleus. He examined the condition of the cells 1, 2, 3, 4, 6, etc., days after the experiment. His description coincides with mine in the essential points, only he speaks of a finely dusted, not of a homogeneous appearance of the diseased parts. Considering that I did not study the process of degeneration at as early stages as he did, I could not give as accurate a statement of the retrogressive changes. Where the degeneration was still in the beginning, I could also frequently observe a finely granulated or dusted appearance of the affected parts. It may be also that the modification which I used gave somewhat less accurate results than Nissl's new methylen blue method.

In the case of amputation which Kahler and Pick have described (vide page 603 of this article) the alterations found in the cells of the anterior horn of the lumbar portion of the cord were evidently of the same nature as those which I described as homogeneous degeneration. I shall mention some details of Kahler and Pick's report which clearly demonstrate this: The affected cells are decidedly enlarged—they appear paler and much more evenly stained—they have a homogeneous colloid appearance—the nuclei with very distinct nucleoli are located quite peripherically and in some sections appear like a projection attached to the cell."

That which makes Kahler and Pick's case especially interesting is that the patient died at as late a period as eighteen years after the amputation. This proves that the homogeneous degeneration can arrest itself at a certain stage and that the cells can preserve themselves for years in the changed condition. It follows that the homogeneous degeneration of a "motor" cell as caused by severance of the continuity of the motor fibre which originates from it does not necessarily lead to complete destruction of the cell even when the continuity of the fibre remains unrestored.

This, furthermore, suggests that in the beginning of homogeneous degeneration the "motor" cell may still be capable of "recovery," if the function of the motor fibre can be restored.

The experimental researches of Lubinow on the regeneration of nerve cells in the cerebral cortex, which had undergone retrogressive changes under the influence of the disturbances of nutrition caused by starvation are very illustrative in that regard. L. could observe the regeneration of cells, the cell-body of which had nearly completely disappeared; the remaining protoplasm accumulates around the nucleus in shape of a narrow border, which becoming broader and broader begins to give off "sprouts" which evidently are the beginning of newly-formed processes.

EXPERIMENT V.—Section of the left ninth intercostal nerve near, and peripherically from the dorsal branch which supplies the muscles of the back. Animal killed six days after the experiment.

Operation performed under ether narcosis. The peripheric stump was loosened somewhat from the underlying tissue, otherwise the stumps were not dislocated.

The animal was very lively and jolly as soon as it recovered from the narcosis. The wound healed by secondary re-union within five days. The cat was killed by chloroform six days after the date of the experiment.

The post-mortem revealed the presence of a jelly-like mass in the region of the operation. The stumps of the severed nerve were embedded in this mass. No pus was present.

I intended to examine the operated nerve by Marchi's method, but had the misfortune to lose it when washing it out after it had been hardened in the mixture of Müller's fluid and osmic acid.

EXAMINATION OF THE SPINAL CORD.

A series of transverse sections was made in such a manner that a continuous series of ten sections were mounted, then the following ten or twenty sections left out, then again ten mounted, etc. Staining with vesuvine in the same manner as in the case just described.

For better recognition of the outlines of the gray matter I left some of the thicker sections overstained. Be it said, however, that the paraffine sections are so ductile and change their shape so easily that the following statements concerning the gross anatomical changes must be taken with due reserve:

PLATE IV.

(Exp. No. V.) Illustrating the alterations which follow the section of an intercostal nerve within six days.

FIG. 1. Photograph showing the dimension of the gray and white matter.

Magnifying power 13 lin. Vesuvine stain. (Overstained section.)

FIG. 2. Photograph showing the distribution of the diseased cells.

Magnifying power 47 lin. Vesuvine stain.

Deg. = District of diseased cells.

Back = Normal cells forming the group for the muscles of the back.

FIG. 3. Water color, showing various stages of the retrogressive cell changes.

Magnifying power 320 lin. Vesuvine stain.

PLATE IV.

FIG. 1.

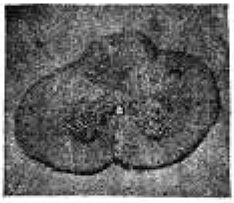


FIG. 2.

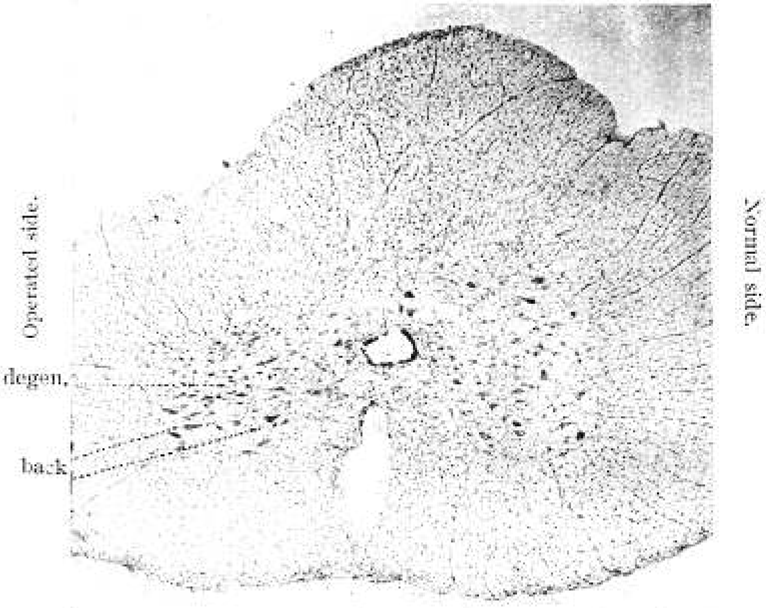


FIG. 3

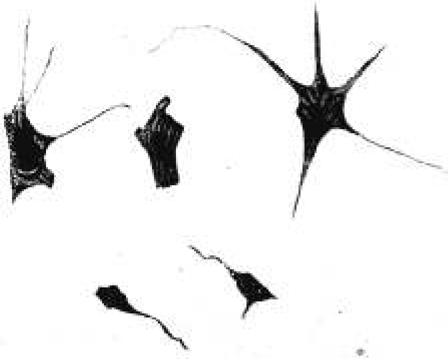


Fig. 1 reduced to $\frac{2}{3}$ of size of original illustration.
Fig. 2 " $\frac{7}{9}$ " " "
Fig. 3 " $\frac{9}{10}$ " " "

The magnifying power is therefore—
For Fig. 1=9 lin. (not 13).
For Fig. 2=37 lin. (not 47).
For Fig. 3=288 lin. (not 320).

The left posterior column is enlarged in frontal direction. The same is the case with the left posterior horn. There does not seem to exist any differences in size between the antero-lateral columns and between the anterior horns. Regarding the anterior roots I dare not make any definite statement as they are too badly contrasted against the surroundings to permit judgment as to their calibre.

I. GANGLIONIC CELLS.

1. Cells of the anterior horns.

There are distinct changes in the multipolar cells of the left anterior horn, but these changes are confined to a certain district which occupies the postero-external part of the anterior horn the cells situated at its anterior and internal border being mostly free from alterations, although also here diseased cells are occasionally met with. Fig. II. of plate IV. will serve to demonstrate the position and extent of the affected district.

The nature of the changes is the following:

The cells are considerably reduced in size. They have a shrunken dried-out appearance. This shrinkage affects all parts of the cell, including the nucleus and processes. To the processes of many cells it gives what Nissl rightly calls a corkscrew-like appearance. On account of their dark color (much darker than in normal cells) and of the hiatus which the shrinkage leaves around them they are better marked against the surrounding tissue than those of normal cells, and can be traced further peripherically.

The affected cells are much more darkly stained than the normal ones. In the beginning stages of the retrogressive process a granulated structure can still be recognized, the granula having an intensely dark tinge, but the granula (corpuscles) are less distinctly marked as the chromatophobe part of the substance of the cell-body is also quite deeply stained, while in normal cells it does not accept the stain. The cells resemble very much the type which Nissl describes as "chromatophile cells."

In many cells in which the shrinkage has become intense, a distinctly folded appearance, similar to that of a dried pear is noticed, in others it seems as if an asbestos-like splitting into rimes had taken place.

As was mentioned, the nucleus is also involved in the shrinkage. It diminishes in size proportionately to the shrinkage of the cell-body, and assumes a dark color which in advanced stages corresponds to that of the cell-body so that its outlines become unrecognizable.

The nucleolus on account of the intensely dark color can still be frequently recognized when the outlines of the nucleus have become lost.

I feel satisfied that the principal characteristics of the observations described are a drying out and subsequent solidification of the cell. This is affirmed by the observation of cells in which one or several processes were found broken off and where the break had a serrated appearance, similar to the break of soft wood.

The said alterations could be seen as early as three days after the section of an intercostal nerve. At least quite a number of cells of the described character were found in the anterior horn of the cat upon which section of an intercostal nerve was performed, and which was killed three days after the experiment. As the series of sections was very incomplete in that case, it did not offer as good an opportunity to study the nature of the changes and the distribution of the diseased cells. In the cat operated upon in the same manner, but which was killed fourteen days after the experiment, the cell alterations, especially the shrinkage, were found much more advanced, a large number of cells had disappeared altogether, others were represented only by dark structureless chunks, others showed an exquisitely dark shrunken and folded appearance with thin, dark, cork-screw-like processes.

I have stated already that in the animal which was killed six days after the experiment (section of the intercostal nerve) the cells of the anterior and internal border of the left anterior horn were mostly found free from alterations. The district of affected cells occupies the central and external part of the left anterior horn. But as I mentioned before, in some sections single diseased cells were also observed at the anterior border of the anterior horn. In a few sections hardly one normal cell was found in the left anterior horn.

In the right anterior horn only few diseased cells were found; here they were not as distinctly grouped as on the other side; sometimes two or three shrunken cells were seen at the anterior border, then again one or two in the centre of the anterior horn, etc.

It must be mentioned that in the left anterior horn the cells which underwent retrogressive changes belong on the average to a smaller type than those which were left free from changes. The diseased cells bear great resemblance to what Nissl calls chromophile cells. As the latter are met with in perfectly normal specimens in varying quantity and structure, N. warns not to mistake them for pathological formations. I must state, however, that in the case described the cells which presented the uncommon characteristics mentioned were so numerous and so typically arranged that to consider them as physiological formations is out of question.

Considering that in the last described experiment the nerve was severed peripherically from the dorsal branch which supplies the muscles of the back, and that the cells situated in the median and anterior part of the left anterior horn remained for the most part normal, it must be concluded that this normal group of cells supplies the muscles of the back. This agrees with the results of Kaiser, who states that the nucleus for the muscles of the back extends as a medial column through the whole length of the spinal cord. In position and extent this " medial group " (or medial column of cells) corresponds to the medial district isolated by the experiment mentioned.

Collins, whose investigations were based upon the examination of the spinal cord of an individual who in his childhood had been affected with poliomyelitis, has come to the same conclusion concerning the function of the medial cell group.

Spitzka's statement that the nearer the muscle is to the dorsal line of the animal, the nearer to the so-called lateral cornu will its nucleus have to be sought for is, therefore, at variance with the findings of these experiments as it was with those of Collins. Furthermore, Spitzka's contention is denied by the fact that in experiment II. where both roots of a dorsal nerve had been severed all cell groups were equally affected, the medial group in no less degree than the others.

2. *Cell alterations of the character described were also found in the group of small cells at the base of the posterior horns.*

The area of diseased cells is situated more cephalad than the area of affected cells in the anterior horns. In many sections nearly every cell of the group at the base of the left posterior horn has undergone retrogressive changes. At the base of the right posterior horn less diseased cells are met with, but still they are quite numerous.

The arrangement of the diseased cells in the course of the medial posterior root bundles makes it certain that the group is intimately connected with the posterior roots. It must also be assumed that part of the cells of this group are connected with the posterior roots of the same side, part with those of the opposite side.

3. Cells of the medial zone (Waldeyer's Mittelzellen).

On the left side many of the cells of this zone have also undergone the described retrogressive changes. On the right side only few altered cells are met with.

4. Cells of Clarke's columns.

The area of diseased cells is situated more cephalad than that of the altered cells of the anterior horns. Numerous cells have undergone the retrogressive changes reported. Besides this the absolute number of cells is diminished. In the group of the left side the alterations are more intense than in that of the right side.

5. Cells of the lateral horn.

In both lateral horns shrunken cells are found; considerably more in the left than in the right one.

II. NEUROGLIA.

In some sections there seems to be a slight increase of the neuroglia elements in the left anterior horn. At any rate it is insignificant and in most of the sections cannot be stated. No signs of inflammation are noticed.

With regard to the localization of the cell alterations there exist some differences in the various experiments. In the spinal cord, which was treated after Marchi's method (section of anterior root of dorsal nerve) numerous degenerated cells were also found in the anterior horn *opposite* to the side of the lesion. In the animal experimented upon in the same manner, except that the spinal cord was treated after Nissl's method, only few degenerated cells were found in the anterior horn opposite to the side of the operation. The same was the case with the cat upon which section of an intercostal nerve had been performed.

This difference is probably due to the fact confirmed also by Nissl that the retrogressive changes do not set in simultaneously in all cells. The reason why more extensive changes of the cells of the right anterior horn (opposite the side of the lesion) were found in the first case (Marchi specimen) is, evidently, that here the retrogressive changes had further advanced and involved a larger number of cells, the animal having been killed four weeks after the date of the experiment, while the other two animals were killed as early as six days after the date of the experiment.

Nissl properly calls attention to the fact that if purulent inflammations follow the operative lesion, many cells will be directly damaged by the inflammation, which would make it very difficult to decide what was the consequence of the inflammation and what the secondary effect of the lesion intended.

For this reason I excluded those cases from a special report in which I suspected that the retrogressive changes due to the interruption of the continuity of the nerve fibres were complicated with changes caused by inflammation.

Nissl confirms Weigert's statement that proliferation of the neuroglia towards the degenerating cardinal tissue (ganglionic cells and nerve fibres) is a normal reaction of the healthy tissue against the weakened one; but he adds that this proliferation varies very much in degree, being, for instance, quite insignificant for certain thalamus nuclei, while in other nuclei of the thalamus it is very intense. I, for my part, observed that the cell changes following the section of dorsal nerves or of their roots were accompanied by very insignificant, if any, proliferation of the neuroglia. It is possible, however, that proliferation of the neuroglia might have been detected at a later period, that is, if the animals had been killed say for instance two months after the experiment.

In summing up we find that the section of an intercostal nerve of a half-grown animal was followed by retrogressive changes both of cells intimately connected with the posterior roots of the severed nerve and of cells which give origin to its motor fibres. These changes could be made out within three days after the date of the injury, but they were more intense six days after the date of the experiment. They were marked by a gradual shrinkage of all parts of the cell accompanied by a modification of its structure and characterized by the increased affinity to certain aniline stains and evidently also by a solidification of its contents. It results from Nissl's observations that these alterations reach their culmination within 18, 22–30 days after the interruption of the continuity of the nerve fibres. The lesion of the structure of the cell is much less deep, and the chance for recovery therefore much greater than in the homogeneous degeneration of the cell. Nissl, has indeed, observed that after the alterations have reached their culmination most of the cells partially recover by means of their lateral connections with other neurons. The chances for recovery of cells will, of course, be still better if the conditions for the regeneration of the peripheric nerve stump are favorable.

Howell and Huber who studied the degeneration and regeneration in peripheral nerve fibres after severance of the connections with their nerve centres, found that in no case a primary union between the fibres of the central and peripheral end took place. In all their experiments "degeneration of the peripheral end was complete throughout its entire length, (an observation confirmed also by Vanlair). The least time in which irritability began to return to parts peripheral to the cut was twenty-one days, and at this time regeneration was found to have progressed some distance beyond the wound."

It is very probable that while the peripheral ends of the severed peripheral nerve fibres undergo degeneration, retrogressive changes take place simultaneously in the nerve cells from which these fibres originate and that when the fibres, or better said, the axis cylinders of the central stump, begin to grow into the peripheric stump, the ganglionic cells also begin to recover.

In Exp. V (section of the intercostal nerve, animal killed six days after the injury) the conditions for regeneration of the nerve were certainly favorable, as the nerve was cut through without dislocation of the ends; still the physiological centres of the injured neurons underwent the retrogressive changes described.

The result of my investigations lead me to the following conclusions:

1. The severance of the continuity of a spinal nerve or of both its roots is always followed by retrogressive changes both in cells which are intimately connected with its posterior roots and in cells from which its motor fibres originate.

2. a. These changes may set in gradually and consist in a gradual shrinkage of all parts of the cell accompanied by a modification of its structure, characterized by in-

creased affinity to certain aniline stains and evidently also by a solidification of its contents.

b. Or the changes may set in acutely, being marked by swelling and homogeneous transformation of the cell contents; this transformation begins in a circumscribed part of the cell-body and then spreading itself towards the periphery, it involves the processes and nucleus.

This transformation may lead to liquefaction and final absorption of the cell, or may arrest itself at a certain stage.

In specimens treated after Marchi's method, the beginning of the homogeneous transformation is marked by swelling and distinct differentiation of all parts of the cell, while normal cells receive a shrunken rudimentary appearance by this method, so that their ganglionic character can hardly be recognized. In later stages of the degeneration the differentiation of the various parts becomes lost.

3. The character of the retrogressive changes is determined.

a. By the distance of the point of lesion from the cell.

b. By the character of the cell, or more probably by the manner of its connection with the severed fibres.

In "motor" cells severance of the motor fibre near origin from the cell (section of the anterior root) is followed by the acute changes, viz. by homogeneous transformation of the cell.

Lesion of the motor fibre at a considerable distance from the cell effects as a rule the gradual changes, that is a gradual shrinkage of the cell; but occasionally, as the case of amputation reported by Kahler and Pick proves, also here the changes in the "motor" cells may have the character of homogeneous degeneration.

In the cells of Clarke's columns, in the small cells situated at the base of the posterior horns, and in those of the lateral horns the changes always bore the character of the gradual shrinkage, no matter whether the nerve (larger distance), or the roots (small distance) was severed. Here the manner of the connection between the severed fibre and the cell which undergoes the change is less intimate than the connection between "motor" cell and motor fibre, as the latter is the principal part of the neuron of which the "motor" cell forms the centre.

4. The gradual shrinkage gives probably much more

chance for recovery of the cell, if the continuity of the severed nerve fibre can be restored, than the homogeneous degeneration.

5. The small cells situated at the base of the posterior horns along the course of the nerve bundles, which pass from the ventral part of the posterior columns towards the lateral columns, are intimately connected with the posterior roots. Part of these cells are connected with posterior root fibres of the same side, part with posterior root fibres of the opposite side. This connection probably consists in close contact of the terminal branches of the posterior root fibre with the network into which the axis cylinder of the altered cell dissolves itself; nothing positive can be stated in that regard, however, without examination by Golgi's or Ramon y Cajal's method. The latter makes no mention of said cells.

6. The cell group of Clarke's columns is in connection with fibres of the posterior roots both of the same and opposite side.

7. Of the cells of the medial zone (Waldeyer's "Mittelzellen"), and of the small cells of the lateral horn, I can only state, that they undergo a shrinkage after the severance of the peripheric nerve or its roots, but cannot decide with which of the roots they are connected.

8. The group of cells which supplies the muscles of the back with motor fibres, occupies the medial and anterior part of the anterior horn, which is in accordance with the views of Kaiser and Collins respecting the function of this group.

In conclusion I wish to recommend warmly Nissl's method of staining as a valuable addition to the methods in use for the investigation of the central nervous system. For the study of the finer structure of ganglionic cells it is much superior to the nigrosine, carmine and similar stains. This superiority is due to the fact stated by Nissl, that the hardening with the chromsalts damages the structure of the cells, for which reason fine cell changes will easily escape observation.

REMARKS CONCERNING ILLUSTRATIONS.

Part of the illustrations are photographs, part of them water colors. The first were made by myself, the latter by my sister under my supervision. The dimensions of the cells in the water colors were measured so as to represent the exact size corresponding to the power used.

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